

We claim:

1. An isolated nucleic acid molecule that includes an open reading frame encoding a protein selected from the group consisting of: MOP2, MOP3, MOP4, MOP5, MOP6 MOP7, MOP8 and MOP9.

2. The nucleic acid molecule of claim 1, which is DNA.

3. The DNA molecule of claim 2, which is a gene, the exons of which comprise said open reading frame encoding said protein.

4. The DNA molecule of claim 2, which is a cDNA.

5. The nucleic acid molecule of claim 1, wherein said open reading frame encodes a protein having an amino acid sequence substantially the same as a sequence selected from the group consisting of SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17 and SEQ ID NO:18.

6. The nucleic acid molecule of claim 5, which comprises a sequence substantially the same as a sequence selected from the group consisting of SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8 and SEQ ID NO:9.

7. An isolated protein which is a product of expression of part or all of the open reading frame of claim 1.

8. A recombinant DNA molecule comprising the nucleic acid molecule of claim 1, operably linked to a vector for transforming cells.

9. An isolated nucleic acid molecule having a sequence selected from the group consisting of:

- a) SEQ ID NO:2;
- b) an allelic variant of SEQ ID NO:2;
- 5 c) a natural mutant of SEQ ID NO:2;
- d) a sequence specifically hybridizing with part or all of a sequence complementary to SEQ ID NO:2 and encoding a polypeptide substantially the same as part or all of a polypeptide encoded by SEQ ID NO:2; and
- 10 e) a sequence encoding part or all of a polypeptide having amino acid SEQ ID NO:11.

10. An isolated nucleic acid molecule having a sequence selected from the group consisting of:

- 15 a) SEQ ID NO:3;
- b) an allelic variant of SEQ ID NO:3;
- c) a natural mutant of SEQ ID NO:3;
- d) a sequence hybridizing with part or all of a sequence complementary to SEQ ID NO:3 and encoding a polypeptide substantially the same as part or all of a polypeptide encoded by SEQ ID NO:3; and
- 20 e) a sequence encoding part or all of a polypeptide having amino acid SEQ ID NO:12.

25 11. An isolated nucleic acid molecule having a sequence selected from the group consisting of:

- a) SEQ ID NO:4;
- b) an allelic variant of SEQ ID NO:4;
- c) a natural mutant of SEQ ID NO:4;
- 30 d) a sequence hybridizing with part or all of a sequence complementary to SEQ ID NO:4 and encoding a polypeptide substantially the same as part or all of a polypeptide encoded by SEQ ID NO:4; and
- e) a sequence encoding part or all of a polypeptide having amino acid SEQ ID NO:13.
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12. An isolated nucleic acid molecule having a sequence selected from the group consisting of:

- a) SEQ ID NO:5;
- b) an allelic variant of SEQ ID NO:5;
- 5 c) a natural mutant of SEQ ID NO:5;
- d) a sequence hybridizing with part or all of a sequence complementary to SEQ ID NO:5 and encoding a polypeptide substantially the same as part or all of a polypeptide encoded by SEQ ID NO:5; and
- 10 e) a sequence encoding part or all of a polypeptide having amino acid SEQ ID NO:14.

13. An isolated nucleic acid molecule having a sequence selected from the group consisting of:

- 15 a) SEQ ID NO:6;
- b) an allelic variant of SEQ ID NO:6;
- c) a natural mutant of SEQ ID NO:6;
- d) a sequence hybridizing with part or all of a sequence complementary to SEQ ID NO:6 and encoding a polypeptide substantially the same as part or all of a polypeptide encoded by SEQ ID NO:6 and
- 20 e.) a sequence encoding part or all of a polypeptide having amino acid SEQ ID NO:15.

25 14. An isolated nucleic acid molecule having a sequence selected from the group consisting of:

- a) SEQ ID NO:7;
- b) an allelic variant of SEQ ID NO:7;
- c) a natural mutant of SEQ ID NO:7;
- 30 d) a sequence hybridizing with part or all of a sequence complementary to SEQ ID NO:7 and encoding a polypeptide substantially the same as part or all of a polypeptide encoded by SEQ ID NO:7; and
- e) a sequence encoding part or all of a
- 35 polypeptide having amino acid SEQ ID NO:16.

15. An isolated nucleic acid molecule having a sequence selected from the group consisting of:

- 5 a) SEQ ID NO:8;
 b) an allelic variant of SEQ ID NO:8;
 c) a natural mutant of SEQ ID NO:8;
 d) a sequence hybridizing with part or all
of a sequence complementary to SEQ ID NO:8 and encoding a
polypeptide substantially the same as part or all of a
polypeptide encoded by SEQ ID NO:8; and
10 e) a sequence encoding part or all of a
polypeptide having amino acid SEQ ID NO:17.

16. An isolated nucleic acid molecule having a sequence selected from the group consisting of:

- 15 a) SEQ ID NO:9;
 b) an allelic variant of SEQ ID NO:9;
 c) a natural mutant of SEQ ID NO:9;
 d) a sequence hybridizing with part or all
of a sequence complementary to SEQ ID NO:9 and encoding a
20 polypeptide substantially the same as part or all of a
polypeptide encoded by SEQ ID NO:9; and
 e) a sequence encoding part or all of a
polypeptide having amino acid SEQ ID NO:17.

25 17. A recombinant DNA molecule comprising the
nucleic acid molecule of any of claims 9-16, operably linked
to a vector for transforming cells.

Sub A1
30 18. An oligonucleotide between about 10 and about
100 nucleotides in length, which specifically hybridizes
with a portion of the nucleic acid molecule of any of claims
~~9-16.~~

35 19. The oligonucleotide of claim 18, wherein said
portion includes a translation initiation site of said
polypeptide.

20. A cell transformed with the recombinant DNA molecule of any of claims 9-16.

5 21. An isolated protein encoded by the nucleic acid molecule of any of claims 9-16.

22. An antibody immunologically specific for part or all of the protein of claim 8.

10 23. An antibody immunologically specific for part or all of the protein of Claim 21.

15 24. An isolated nucleic acid molecule comprising a sequence that encodes an α -class hypoxia-inducible factor, said factor being encoded by a gene located on human chromosome 19q13.13-13.2.

20 25. A polypeptide encoded by the nucleic acid molecule of claim 24, which is produced in mammalian adult thymus, lung, brain, heart and kidney.

26. The polypeptide of claim 25, having amino acid SEQ ID NO:16.

25 27. An isolated nucleic acid molecule comprising a sequence that encodes an α -class hypoxia-inducible factor, said factor being encoded by a gene located on human chromosome 2p16-21.

30 28. A polypeptide encoded by the nucleic acid molecule of claim 27, which is produced in mammalian vascular endothelial cells.

35 29. The polypeptide of claim 28, having amino acid SEQ ID NO:11.

30. An isolated nucleic acid molecule comprising a sequence that encodes a circadian-responsive factor that heterodimerizes with a binding partner and stimulates transcription of genes having an E-box transcription control element comprising a sequence CACGTGA.

31. The nucleic acid molecule of claim 30, wherein said sequence encodes a protein having an amino acid sequence substantially the same as a sequence selected from the group consisting of SEQ ID NO:13 and SEQ ID NO:17.

32. The nucleic acid molecule of claim 30, which comprises a sequence substantially the same as a sequence selected from the group consisting of SEQ ID NO:4 and SEQ ID NO:8.

33. An isolated protein, which is a product of expression of part of all of the nucleic acid molecule of claim 30.

34. A recombinant DNA molecule comprising the nucleic acid molecule of claim 30, operably linked to a vector for transforming cells.

35. An isolated nucleic acid molecule comprising a sequence that encodes a binding partner for a circadian-responsive factor that heterodimerizes with said binding partner and stimulates transcription of genes having an E-box transcription control element comprising a sequence CACGTGA.

36. The nucleic acid molecule of claim 35, wherein said sequence encodes a protein having an amino acid sequence substantially the same a sequence selected from the group consisting of SEQ ID NO:12 and SEQ ID NO:18.

37. The nucleic acid molecule of claim 35, which comprises a sequence substantially the same a sequence selected from the group consisting of SEQ ID NO:3 and SEQ ID NO:9.

38. An isolated protein, which is a product of expression of part of all of the nucleic acid molecule of claim 35.

39. A recombinant DNA molecule comprising the nucleic acid molecule of claim 35, operably linked to a vector for transforming cells.

40. A method for determining if a test compound regulates circadian function, which comprises the steps of:

a) providing a recombinant cell comprising:

i) a heterologous nucleic acid molecule encoding an expressible circadian-responsive factor that forms a heterodimer with a binding partner and stimulates transcription of genes having an E-box transcription control element comprising a sequence CACGTGA;

ii) a heterologous nucleic acid molecule encoding the binding partner for the circadian-responsive factor; and

iii) a reporter gene comprising at least one transcriptional control element having a sequence CACGTGA, operably linked to a reporter coding sequence, the expression of said gene being induced by binding of said heterodimer to said transcriptional control element;

b) preparing a culture of the recombinant cells;

c) incorporating the test compound into the cell culture under conditions permitting expression of the heterologous nucleic acid molecules, heterodimerization of the factor and the binding partner, and binding of the heterodimer to the transcriptional control element;

e) measuring expression of the reporter gene and comparing the expression to an equivalent cell culture in which the test compound was not incorporated, a change in expression of the reporter gene in the culture containing the test compound being indicative of the ability of the test compound to regulate circadian function.

41. The method of claim 40, wherein the circadian-responsive factor is MOP4 and the binding partner is MOP3.

42. A method for determining if a test compound regulates red blood cell synthesis, glucose metabolism or angiogenesis, which comprises the steps of:

a) providing a recombinant cell comprising:

i) a heterologous nucleic acid molecule encoding an expressible α -class hypoxia-responsive factor that forms a heterodimer with a binding partner and stimulates transcription of genes having a hypoxia responsive transcription control element (HRE);

ii) a heterologous nucleic acid molecule encoding the binding partner for the hypoxia-responsive factor; and

iii) a reporter gene comprising at least one transcriptional control element having a sequence CACGTGA, operably linked to a reporter coding sequence, the expression of said gene being induced by binding of said heterodimer to said HRE;

b) preparing a culture of the recombinant cells;

c) incorporating the test compound into the cell culture under conditions permitting expression of the heterologous nucleic acid molecules, heterodimerization of the factor and the binding partner, and binding of the heterodimer to the HRE;

e) measuring expression of the reporter gene and comparing the expression to an equivalent cell culture in which the test compound was not incorporated, a change in expression of the reporter gene in the culture containing the test compound being indicative of the ability of the test compound to regulate red blood cell formation, glucose metabolism or angiogenesis.

43. The method of claim 42, wherein the hypoxia-responsive factor is selected from the group consisting of MOP1, MOP2, MOP6 and MOP7.

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